NSIC

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration

Center for Biologics Evaluation and Research
1401 Rockville Pike
Rockville MD 20852-1448

JAN 24 2007

Notice of Initiation of Disqualification Proceeding
And Opportunity to Explain

By Certified Mail – Return Receipt Requested
And By Facsimile Transmission

Daniel Bigg
Chicago Recovery Alliance
400 East Ohio Street, Suite 3103
Chicago, Illinois 60611

Dear Mr. Bigg:

The Food and Drug Administration (FDA, or the Agency) has investigated allegations that you failed to fulfill the responsibilities of a clinical investigator for studies involving HIV rapid tests in violation of FDA regulations governing investigational devices. FDA Investigator Russell Riley from the Chicago District Office met with you during two inspections and reviewed the records relating to the use of two investigational HIV rapid test kits. The first inspection was conducted from February 8 through February 28, 2005 and focused on your conduct of a clinical study entitled [redacted] *HIV Clinical Trial - Protocol #*[redacted] hereafter referred to as Study 1. The second inspection starting March 16, 2005 was completed August 2, 2005, and focused on your conduct of a clinical study entitled [redacted], hereafter referred to as Study 2. FDA conducted these inspections under the agency's Bioresearch Monitoring Program which includes inspections designed to review the conduct of research involving investigational devices.

At the end of each inspection, a Form FDA 483, Inspectional Observations, was issued and discussed with you. You responded in a letter to FDA dated March 20, 2005, for Study 1, but the Agency received no letter in response to the Form FDA 483 issued to you for Study 2. Our comments on the violations are set forth below. This letter includes violations based on the two Form FDA 483s, as well as additional violations, and provides the opportunity for you to explain those violations.

Based on the results of the two inspections and other information available to the Agency, we believe that you repeatedly or deliberately violated regulations governing the proper conduct of clinical studies involving investigational devices, and repeatedly or deliberately submitted false information to the sponsors of the investigations, all in violation of Title 21, Code of Federal Regulations (CFR), Parts 50 and 812. The regulations are available at http://www.gpoaccess.gov/cfr/index.html.

This letter provides you with written notice of the matters under complaint and initiates an administrative proceeding, described below, to determine whether you should be entitled to receive investigational devices, as set forth in 21 CFR § 812.119.

A listing of the violations follows, and the applicable provisions of the CFR are cited.

1. **You repeatedly or deliberately submitted false information to the sponsors. [21 CFR § 812.119(a)].**

   As shown in the table below, you allowed nine Study 1 subjects and nineteen Study 2 subjects to participate twice (and in one instance, three times) in their respective studies under different subject numbers. You submitted all the data regarding these subjects to their respective study sponsor. This skewed whatever results were obtained, namely, that these results became a disproportionate fraction of the data, in effect twice, or three times, the fraction size that they should have been. Therefore, the number of enrolled subjects, and any calculations based on this number, such as sensitivity and specificity, became invalid for your site as a result.

Subject	Study	Subject #	Date of Consent/Test
	1		1/18/04
			2/1/04
	1		1/25/04
			3/28/04
	1		2/6/04
			2/17/04
	1		2/14/04
			3/30/04
	1		2/15/04
			2/17/04
	1		2/17/04
			3/30/04
	1		2/17/04
			3/30/04
	1		2/17/04
			3/30/04
	1		2/17/04
			3/30/04
	2		12/16/01
			1/20/02
			1/27/02
	2		12/10/01
			1/14/02
	2		1/13/02
			5/19/02
	2		12/19/01
			2/6/02

	2		12/10/01
			5/13/02
	2		Consented 1/2/02 Tested 1/4/02
			1/14/02
	2		1/4/02
			1/14/02
	2		1/13/02
			2/17/02
	2		12/19/01
			2/6/02
	2		1/2/02
			5/1/02
	2		12/14/01
			5/13/02
	2		12/19/01
			2/6/02
	2		1/13/02
			4/21/02
	2		12/16/01
			2/3/02
	2		4/21/02
			5/26/02
	2		1/2/02
			5/22/02
	2		1/2/02
			1/9/02
	2		1/13/02
			5/19/02
	2		5/8/02
			5/15/02

Indeed, in your letter of March 20, 2005, you admitted that subjects participated in Study 1 on more than one occasion: "In the future, procedures will be put in place to assure that people are not allowed to participate in the study twice. I was trying to prevent this but only in my head and we will implement procedures to control this in the future."

2. **You failed to ensure that the investigations were conducted according to the investigational plan, the signed agreement, applicable FDA regulations, and conditions of approval imposed by the IRB or FDA, this, in order to protect the rights, safety, and welfare of the subjects under your care. [21 CFR §§ 812.100, 812.110(a),(b), and 812.119(a)].**

   A. You enrolled more subjects in Study 2 than were permitted by the protocol and by the conditions of the IRB approval.

The testing plan in the Study 2 protocol specifies that your site was authorized to enroll 200 high risk subjects. However, our investigation reveals that there were 411 completed subject consent forms, one of which was a repeat (subject was retested and then identified as). You also enrolled 19 subjects more than once for a total of 39 test results, identifying those 19 subjects with a different number and considering them to be new participants. According to this information, the actual number of high risk subjects enrolled in Study 2 was 390.

B. You involved human subjects in research prior to Institutional Review Board (IRB) approval of the consent form for Study 2. The Institutional Review Board, reviewed and approved the protocol for Study 2 on 11/21/01. However, your consent form and your site, the Chicago Recovery Alliance Mobile Van, were not approved until 12/28/01. As shown in the table below, you enrolled, obtained the consent of, and tested 107 subjects prior to the date the IRB approved your consent form and your site.

Study 2 Subject(s)	# of Subjects	Date of Consent/Test
	7	12/10/01
	6	12/12/01
	8	12/13/01
	1	Consented 12/13/01 Tested 12/14/01
	14	12/14/01
	12	12/16/01
	16	12/17/01
	11	12/19/01
	19	12/20/01
	13	12/21/01

C. Protocol sections 8.0 and 9.0 of both Study 1 and Study 2 require that enrolled subjects be between the ages of 18 and 55 years and be able to sustain venipuncture. Subjects with life threatening illnesses (with the exception of HIV, AIDS, or viral infections), as well as those with suppressed immune systems, were to be excluded from the study.

i. You failed to verify that the subjects you enrolled in Study 1 met the enrollment criteria of health status and age.

In your letter, you claim that the Study 1 high risk subjects were in fact screened for age and life threatening illnesses, but you acknowledge the lack of documentation of the assessments. You do not address whether subjects were screened for immunosuppression. You also claim that a retrospective date of birth search was conducted, and based on your list you acknowledge that two subjects did not meet the age requirement.

ii. You failed to verify the ages or dates of birth for 89 subjects you had enrolled in Study 2.

iii. Review of the remaining Study 2 records shows that you enrolled sixteen subjects who did not meet the age requirements. Subjects [redacted] and [redacted] were enrolled although these subjects were under the protocol required age of 18, and fourteen enrolled subjects exceeded the age limit of 55.

Study	Subject	Age
Study 2	[redacted]	60
Study 2	[redacted]	64
Study 2	[redacted]	72
Study 2	[redacted]	58
Study 2	[redacted]	17
Study 2	[redacted]	58
Study 2	[redacted]	62
Study 2	[redacted]	16
Study 2	[redacted]	58
Study 2	[redacted]	57
Study 2	[redacted]	64
Study 2	[redacted]	57
Study 2	[redacted]	63
Study 2	[redacted]	60
Study 2	[redacted]	60
Study 2	[redacted]	57

D. Study 2 protocol section 15.0 requires that controls be run daily, at a minimum. This means that for each day of testing, the same [redacted] lot number must be used for testing both the subject(s) and the controls. As shown in the table below, 47 Study 2 subjects were tested on eight days with [redacted] lot numbers that were tested without controls or with inappropriate controls on that same day. Indeed, there is no evidence that lots [redacted] were tested with controls at any time during the study.

Date	Study 2 Subject(s)	Subject(s) Tested with Lot #:	Controls Tested with Lot #:	# of Subjects
4/14/02	[redacted]	[redacted]	[redacted]	1
5/5/02				6
5/8/02				5
5/12/02				6
5/14/02				7
5/15/02				10
5/16/02				6
5/19/02				6

E. According to Study 2 protocol section 13.0 a sponsor "representative will visit each site and train personnel according to a standardized procedure." The Clinical Trial Training Log documents that the monitor trained you and [redacted] on 12/16/01. However, prior to the training, you and your staff enrolled and tested 36 subjects in Study 2 as shown in the table below.

Date Tested	Study 2 Subjects	# of Subjects
12/10/01	[redacted]	7
12/12/01		6
12/13/01		8
12/14/01		15

F. You permitted eight individuals to assist in the conduct of Study 2 even though they were not trained as required by the protocol. As shown in the table below, these individuals conducted, in total, 70 consent discussions and initialed 182 counseling forms despite not having been trained.

Initials	Last Name	Consent Forms	Counseling Form Entries
[redacted]			
			25
			23
			14
			54
			65
			1

G. You violated Study 1 protocol sections 7.3, 7.4, and 10.0 which require that subjects will be advised of their results and provided with the required counseling regarding the confirmation tests. Although you initialed and dated 52 [redacted] Laboratory Results Forms with reactive results there is no evidence that you actually provided counseling for any of these 52 Study 1 subjects. Although phone numbers were available in your records for most of the study participants, when asked why you didn't call the subjects to arrange counseling, you stated simply that you were not sure if all of them would be valid numbers.

In your letter, you admit the lack of counseling documentation for Study 1 subjects: "Upon initial informed consent and when rapid test results were provided to participants they were counseled that the test result needed to be confirmed and were advised that they needed to return to receive the reference test results.... Documentation of these counseling steps and content was not done as part of this study and I can specifically do this in future efforts again by creating a form which details and records such actions."

Similarly, you violated Study 2 protocol section 7.3 which requires that the clinical investigator will "assure that all study results are reported to the study participants and those participants receive appropriate follow-up counseling.... Once confirmation testing is available, the [clinical investigator] will notify the participant of the results and be responsible for assuring that all required follow-up counseling is provided." There is no evidence that you notified subjects who had reactive rapid tests, and recalled subject for confirmation testing and counseling due to discordant results.

3. **You failed to maintain accurate, complete and current records of each subject's case history, including data on the condition of each subject upon entering, and during the course of, the investigation. You failed to maintain accurate, complete and current records relating to correspondence with the sponsor and monitor, the receipt, use, and disposition of devices, and other required records relating to your participation in the studies. [21 CFR §§ 812.140(a)(1), (2), (3) and (5)].**

A. Individuals participating in Study 1 were required to be between the ages of 18 and 55. In your response letter dated March 20, 2005, you admit that subjects' ages were not recorded at the time of enrollment. After Study 1 was closed, you admit to retrospectively developing the table entitled "Participant Date of Birth List" with all of the subjects' birthdates and ages. We have concluded that the data in this table are false and misleading, based on the following observations:

i. Each of the nine subjects who were enrolled twice under different subject numbers, described in item 1 above, have different dates of birth listed on the table.

Subject	Study 1 Subject #	Date of Consent/Test	Date of Birth on Table	Age
		1/18/04		36
		2/1/04		18
		1/25/04		22
		3/28/04		36
		2/6/04		26
		2/17/04		38

[redacted]	2/14/04	[redacted]	33
	3/30/04		29
	2/15/04		23
	2/17/04		50
	2/17/04		42
	3/30/04		37
	2/17/04		46
	3/30/04		38
	2/17/04		46
	3/30/04		46
	2/17/04		23
	3/30/04		33

ii. Both you and your sub-investigator were enrolled as study subjects in Study 1, and the table you provided incorrectly reports your own birthdates and ages.

Subject	Study 1 Subject #	Date of Consent/Test	Participant's Recorded Date of Birth and Age		Participant's Correct Date of Birth
			Date of Birth	Age	
[redacted]					

iii. Three subjects participated in both Study 1 and Study 2, and as shown in the table below, the birthdates recorded for the three subjects are different for each study. The discrepancies range from 8 to 16 years. The dates of birth and ages shown in the table below for the Study 1 subjects are from your "Participant Date of Birth List." The dates of birth and ages shown in the table below for the Study 2 subjects are from their consent form file folders.

Subject	Study/ Subject #	Date of Consent/Test	Date of Birth/ Age	Date of Birth/ Age
[redacted]	Study 1/	1/25/04	DOB: Age: 20	[redacted]
	Study 2/	1/13/02	[redacted]	Age: 36 Birth year: 1965
	Study 1/	2/17/04	DOB: Age: 24	[redacted]
	Study 2/	12/13/01	[redacted]	Age: 39 Birth year would be 1961 or 1962
	Study 1/	3/30/04	DOB Age: 54	[redacted]
	Study 2/	1/20/02	[redacted]	Age: 46 Birth year: 1955

B. You failed to maintain appropriate records regarding the health status and age of subjects in both Study 1 and Study 2. See item 2C above.

C. You failed to maintain a copy of your signed investigator agreement for Study 2.

D. You failed to document whether Study 2 subjects were tested with [redacted]ot numbers that were also tested with controls on that same day. In addition, you failed to provide documentation showing whether three lots were tested with controls at any time during the study. See item 2D above.

E. You failed to maintain documentation showing whether rapid test counseling was provided for Study 1. For Study 2 you failed to provide documentation as to whether counseling was provided for five subjects. See item 2G above.

F. You failed to maintain shipping records for samples you shipped to the Central Reference Laboratory for Study 2.

4. **You repeatedly or deliberately failed to obtain informed consent. [21 CFR §§ 50, 812.100 and 812.119(a)].**

You failed to obtain informed consent prior to the enrollment and testing of subjects [redacted] in Study 2. None of these subjects signed or dated an informed consent document.

On the basis of the above listed violations, FDA asserts that you have repeatedly or deliberately failed to comply with the cited regulations, and repeatedly or deliberately submitted false information to the sponsors. Accordingly, FDA proposes that you be disqualified as a clinical investigator. You may reply to the above stated issues, including an explanation of why you believe you should remain eligible to receive investigational devices and not be disqualified as a clinical investigator, in a written response or at an informal conference. This procedure is provided for by regulation 21 CFR § 812.119(a).

Within fifteen (15) days of receipt of this letter, write to me to arrange a conference time or to indicate your intent to respond in writing. Your written response must be forwarded within thirty (30) days of receipt of this letter. Your reply should be sent to:

Mary A. Malarkey
Director
Office of Compliance and Biologics Quality (HFM-600)
Center for Biologics Evaluation and Research
Food and Drug Administration
1401 Rockville Pike
Rockville, Maryland 20852-1448

Should you request an informal conference, we ask that you provide us with a full and complete explanation of the above listed violations. You should bring with you all pertinent documents, and you may be accompanied by a representative of your choosing. Although the conference is informal, a transcript of the conference will be prepared. If you choose to proceed in this manner, we plan to hold such a conference within thirty (30) days of your request.

At any time during this administrative process, you may enter into a consent agreement with FDA regarding your future use of investigational devices. Such an agreement would terminate this disqualification proceeding. Enclosed you will find a proposed agreement between you and the Center. The Center will carefully consider any oral or written response. If your explanation is accepted by the Center, the disqualification process will be terminated. If your written or oral response to our allegations is unsatisfactory, or we cannot come to terms on a consent agreement, or you do not respond to this notice, you will be offered the opportunity to request a regulatory hearing before FDA, pursuant to 21 CFR Part 16 (available at the Internet address identified at the bottom of page 1 of this letter) and 21 CFR § 812.119. Before such a hearing, FDA will provide you notice of the matters to be considered, including a comprehensive statement of the basis for the decision or action taken or proposed, and a general summary of the information that will be presented by FDA in support of the decision or action. A presiding officer, free from bias or prejudice, and who has not participated in this matter, will conduct the hearing. Such a hearing will determine whether or not you will remain entitled to receive investigational devices. You should be aware that neither entry into a consent agreement nor pursuit of a hearing precludes the possibility of a corollary judicial proceeding or administrative remedy concerning these violations.

Sincerely,

Mary A. Malarkey

Mary A. Malarkey
Director
Office of Compliance and Biologics Quality
Center for Biologics Evaluation and Research

Enclosures: Proposed consent agreement